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| 09/224,683 | 12/31/1998 | KRISZKINA M. ZSEBO | 01017.35136 | 3460 |

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| EXAMINER |
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 16 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/224,683 | ZSEBO ET AL. | |
| | Examiner | Art Unit | |
| | Bridget E. Bunner | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *71-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

### *Continued Prosecution Application*

The Request for Continued Examination (RCE) filed on 20 September 2002 (Paper No. 14) under 37 CFR 1.114 based on parent Application No. 09/24,683 is acceptable and an RCE has been established. An action on the RCE follows.

### *Status of Application, Amendments and/or Claims*

The amendment of 20 September 2002 (Paper No. 15) has been entered in full. Claims 91-102 and 104 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 71-114 are under consideration in the instant application.

### *Withdrawn Objections and/or Rejections*

1. The objection to claim 104 regarding a missing "." at pg 3 of the previous Office Action (Paper No. 12, 20 March 2002) and pg 5 of the Office Action of 20 July 2001 (Paper No. 9) is *withdrawn* in view of the amended claim (Paper No. 15, 20 September 2002).

2. The rejection of claims 71-114 under 35 U.S.C. § 112, second paragraph at pg 10 of the previous Office Action (Paper No. 12, 20 March 2002) is *withdrawn* in view of the amended claims (Paper No. 15, 20 September 2002).

### *Double Patenting*

3. The rejection of claims 71-114 under obviousness-type double patenting as being unpatentable over claims in U.S. Patent No. 6,204,363 at pg 2-4 of the Office Action of 20 July

2001 (Paper No. 9) is maintained and held in abeyance until an executed terminal disclaimer is filed. Please see New Double Patenting, below.

***Specification***

4. The objection to the specification regarding sequence compliance, priority, the Brief Description of Drawings, and references to other patent applications is maintained and held in abeyance until all other issues are resolved (see Office Action of 20 July 2001, Paper No. 9). However, Applicant is encouraged to submit the appropriate corrections at Applicant's earliest convenience so that the Examiner can approve of the corrections.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim 71 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim reads on a product of nature in that the claimed polypeptide is not "isolated". Amending the claims to read "isolated" would be remedial.

***New Double Patenting***

6. Claims 71-78 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9, 15, 28-30, 40, and 48-51 of copending Application No. 09/643,652. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a polypeptide comprising all or parts of the amino acid sequence of human stem cell factor, wherein the polypeptide is the product of the expression in a prokaryotic or eukaryotic host cell.

It is noted that a compound and all of its properties are inseparable; they are one and the same thing. Furthermore, the subgenus claims of Application No. '652, drawn to a polypeptide comprising part or all of the amino acid sequence of SCF as set forth in Figure 15B, 15C, 42, or 44 render obvious the genus claims 71-73 of the instant application, drawn to a composition comprising SCF polypeptide and any fragments thereof. Additionally, claims 74-78 of the instant application, drawn to specific fragments of the SCF polypeptide, are considered to be a species of the subgenus claims of the '653 application. Therefore, the instant claims reciting a composition which comprises a therapeutically effective amount of stem cell factor polypeptide or biologically active fragment or analog thereof are not patentably distinct over the claims of copending Application No. 09/643,652.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 112, first paragraph***

7. Claims 71-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition which comprises an effective amount of full length mammalian stem cell factor (SCF) polypeptide or a specific fragment of human SCF that enhances hematopoiesis and one or more cytokines in a pharmaceutically acceptable carrier and wherein the composition is effective to treat hematopoietic disorders, does not reasonably provide enablement for a composition which comprises a therapeutically effective amount of SCF or biologically active fragment or analog thereof and one or more cytokines in a pharmaceutically acceptable carrier wherein the composition is effective to treat epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, and germ cell

disorders. Further, the specification, while being enabling for the SCF polypeptide consisting of the amino acid sequence of 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-162, 1-163, 1-164, 1-165, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 of SEQ ID NOs: 46, 61, and 63, does not reasonably provide enablement for the SCF polypeptide consisting of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, as set out in Figures 42A-C and 44A-C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 3-7 of the previous Office Action (Paper No. 12, 20 March 2002) and pg 5-9 of the Office Action of 20 July 2001 (Paper No. 9).

Applicant's arguments (Paper No. 15, 20 September 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the specification of the instant application teaches how to monitor the *in vitro* activity of a given SCF polypeptide and that it was a matter of routine experimentation to set up one or more of these assays to elucidate the effect of a given factor. Applicant also argues that the specification provides specific teachings of how to monitor the effects of a SCF composition *in vivo*. Applicant contends that Example 28 goes on to expressly list the numerous SCF analogs and fragments that have been made. Applicant submits that the teachings in the specification provide specific and substantial guidance to those of skill in the art of how to set up, perform, and evaluate assays designed to determine whether a given SCF has a desired activity. Applicant states that it would be a matter of routine experimentation to run

these and any other fragments and analogs of SCF through any of the battery of assays exemplified in the specification to determine the specific activity of such fragments and analogs.

Applicant's arguments have been fully considered but are not found to be persuasive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". Specifically, since the specification does not teach all possible "biologically active" fragments and analogs of the SCF polypeptide, undue experimentation would be required of the skilled artisan to determine how to use a "biologically active" fragment or analog. The specification of the instant application also does not teach any methods or working examples that indicate which specific activity is associated with a "biologically active" fragment. Although the specification may teach those of skill in the art of how to set up, perform, and evaluate assays, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, the specification of the instant application does not teach SCF fragments consisting of amino acids 1-100, 1-110, 1-120, 1-123, 1-127, as set out in Figures 42A-C and 44A-C. SCF fragments consisting of the amino acids 1-130, 1-131, etc. of SEQ ID NOs: 46, 61, 63 support a genus to a fragment that enhances hematopoiesis. However, the specification at page 185, lines 23-26 guides the skilled artisan that at least 1-130 amino acids of SCF are required for the activity of enhancement of hematopoiesis. The specification does not disclose that SCF fragments shorter than 130 amino acids have any specific activity. Therefore,

undue experimentation would be required of one skilled in the art to determine if all SCF fragments under 130 amino acids have any activity and if so, what that activity is.

Furthermore, the specification teaches that the present invention "provides DNA sequences coding for polypeptide analogs or derivatives of SCF which differ from naturally occurring forms in terms of the identity or location of one or more amino acid residues (i.e., deletion analogs containing less than all of the residues specified for SCF; substitution analogs, wherein one or more residues specified are replaced by other residues; and addition analogs wherein one or more amino acid residues is added to a terminal or medial portion of the polypeptide) and which share some or all of the properties of naturally-occurring forms" (pg 18, lines 31-36; pg 19, lines 1-5). However, the specification of the instant application does not teach all analogs of the SCF polypeptide. The structure and function of every SCF analog claimed is not disclosed in such a manner such that the skilled artisan could make and use them without undue experimentation. As explained in the previous Office Action (Paper No. 12, 20 March 2002), while it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence

data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change, and the nature and extent of changes that can be made in these positions. Although the Applicant points out that the specification teaches art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate the infinite number of SCF analogs recited in the claims and to screen them for a desired activity. Such trial and error is considered undue.

(ii) Applicant argues that enablement is not precluded by the necessity for some experimentation because it is inevitable that there may be some quantity of experimentation required. Applicant indicates that the mere fact that some degree of experimentation is required is not the determinative factor in the scope of enablement and that it is only when the level of experimentation becomes undue that it is fatal to the enablement of an invention. Applicant states that the present specification provides not only a reasonable but a copious amount of guidance to one of skill in the art to who wants to determine the SCF specific activity of an analog, fragment, or derivative. Applicant also contends that a specification disclosure need not teach, and preferably should omit, what is well known to those of skill in the art. Applicant argues that as long as the specification contains at least one method of making and using the claimed invention, then the enablement requirement under 35 U.S.C. § 112 is satisfied.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as mentioned above, although the Applicant points out that the specification teaches art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate the infinite number of SCF analogs recited in the claims and to screen them for a desired activity. Such trial and error is considered undue. Additionally, the specification does not define the specific biological activity associated with SCF fragments. Therefore, undue experimentation would also be required of the skilled artisan to determine the biological activity that is associated with the claimed SCF derivatives.

(iii) Regarding the structure and function of SCF fragments and analogs, Applicant asserts that an example may be a working or prophetic example and that the specification need not contain an example at all if the invention is otherwise disclosed in such a manner that one of skill in the art will be able to practice it without undue experimentation.

Applicant's arguments have been fully considered but are not found to be persuasive. The recitation in the claims of a SCF fragment with any biological activity or any analog is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. The specification does not define a specific activity for the "biologically active" SCF fragment and the skilled artisan must resort to trial and error experimentation to generate the infinite number of SCF analogs recited in the claims and to

screen them for a desired activity. Such trial and error experimentation is considered undue. One skilled in the art would also not be able to predict the activity of a "biologically active" fragment, what fragments encompass this activity, or the structure and function of the infinite number of SCF analogs recited in the claims.

(iv) Applicant argues that a skilled person would be able to predict that variants and analogs of the instant application would have the same functional activities as the human SCF fragments. Applicant indicates that the specification teaches the activity of both human and rat SCF. Applicant states that the skilled artisan sets up the assays as described in the specification and obtains the functional read-out. Applicant contends that given that the specification has taught how to do this for the full length rat and human SCF sequences and for at least 10 fragments of the SCF, there is no factual or scientific reason for why additional fragments could not be assayed in the same fashion to yield the same or similar results.

Applicant's arguments have been fully considered but are not found to be persuasive. The specification may teach those of skill in the art of how to set up, perform, and evaluate assays, this is not adequate guidance, but this is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Although the specification teaches the methodology and results of assays for other fragments of SCF, the specification does not teach SCF fragments consisting of amino acids 1-100, 1-110, 1-120, 1-123, 1-127, as set out in Figures 42A-C and 44A-C. SCF fragments consisting of the amino acids 1-130, 1-131, etc. of SEQ ID NO: 61 supports a genus to a fragment that enhances hematopoiesis. However, the specification at page 185, lines 23-26 guides the skilled artisan that at least 1-130 amino acids of human SCF

are required for the activity of enhancement of hematopoiesis. The specification does not disclose that SCF fragments shorter than 130 amino acids have any specific activity. Therefore, undue experimentation would be required of one skilled in the art to determine if all SCF fragments under 130 amino acids have any activity and if so, what that activity is. Many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Therefore, one skilled in the art cannot predict that the human SCF fragments comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127 of SEQ ID NOs: 46, 61, and 63 or any variants or "analogs" of the instant application will have the same functional activities as the human SCF fragments comprising 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-162, 1-163, 1-164, 1-165, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 of SEQ ID NOs: 46, 61, and 63, since deletions, substitutions, and additions of amino acid residues can often destroy activity of a protein.

(v) Applicant argues that the specification teaches that SCF has a central role in embryogenesis and hematopoiesis and demonstrates its capacity for treatment of various stem cell deficiencies.

Applicant's arguments have been fully considered but are not found to be persuasive. It is noted to Applicant that the recitation of a SCF composition effective to treat epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, and germ cell disorders is interpreted as an intended use. The specification does not disclose any methods or working examples of administering any SCF/cytokine composition to treat any disorder other than a hematopoietic disorder. Undue experimentation would be required of one skilled in the art to determine the efficacy of treatment of numerous diseases after administration of the SCF/cytokine composition. The specification also does not teach the skilled artisan the optimal dosage, duration, and mode of administration of the composition comprising a SCF polypeptide/cytokine. Furthermore, the claimed composition may not necessarily treat epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, or germ cell disorders. Such trial and error experimentation is considered undue.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate the "biologically active" derivatives or "analogs" recited in the claims, to determine the specific activity of a polypeptide fragment, and to determine the efficacy of treatment, the lack of direction/guidance presented in the specification regarding which structural features that are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

8. Claims 71-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth at pg 8-10 of the previous Office Action (Paper No. 12, 20 March 2002) and pg 9-11 of the Office Action of 20 July 2001 (Paper No. 9).

Claims 71-114 recite a therapeutically effective amount of SCF or biologically active fragment or analog thereof and one or more cytokines in a pharmaceutically acceptable carrier wherein the composition is effective to treat hematopoietic disorders, epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, and germ cell disorders. The claims also recite that the SCF polypeptide consists of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 as set out in Figures 42A-C and 44A-C.

Applicant's arguments (Paper No. 15, 20 September 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant argues that there is adequate written description in the specification for numerous other fragments that were made and in the possession of the Applicant before the application was filed. Applicant refers the examiner to pages 182-185 of the specification. Applicant states that the burden of showing possession of many analogs has been met. Applicant also indicates that in light of the numerous recitations in the specification and sequence listing, it

is reasonable that one of skill in the art could and would envision the detailed structure and function of the SCF polypeptide fragments and analogs encompassed by the claims.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed above, Applicant has not provided evidence to demonstrate that the skilled artisan would be able to envision the detailed structure of the infinite number of SCF analogs or SCF fragments with all possible biological activities recited in the claims. The scope of the claims include numerous structural variants. Although the specification discloses the structure and function of numerous SCF fragments, these descriptions are not a representative number to support the description of an entire genus of functionally equivalent SCF biologically active fragments or analogs, which incorporate all SCF mutants, derivatives, and fragments. Therefore, only a human SCF fragment that enhances hematopoiesis and wherein the human SCF polypeptide consisting of the amino acid sequence of 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-162, 1-163, 1-164, 1-165, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 of SEQ ID NOs: 46, 61, and 63, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Furthermore, the broad brush discussion of making or screening for variants does not constitute a disclosure of a representative number of members. The specification's general discussion of making and screening for variants constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed variants.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
November 25, 2002